JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Selective Aryne Formation via Grob Fragmentation from the [2+2] Cycloadducts of 3-Triflyloxyarynes

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Supporting Information

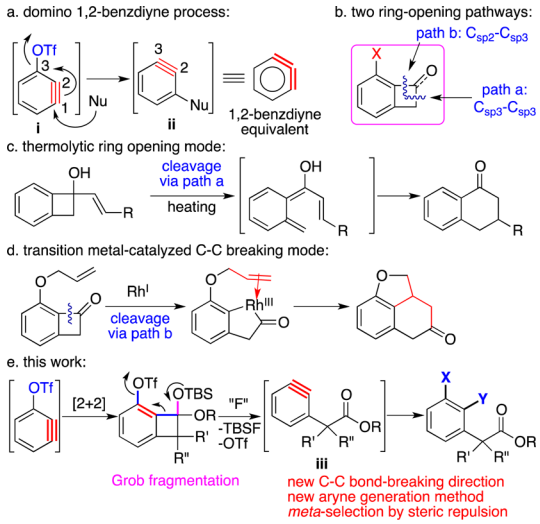
ABSTRACT: A chemoselective ring-opening protocol of the formal [2+2] cycloadducts of 3-triflyloxyarynes was developed to generate 2,3-aryne intermediate via Grob fragmentation. A variety of 1,3-di- and 1,2,3-trisubstituted arenes could be readily accessed through this [2+2] cycloaddition-2,3-aryne formation sequence. The regioselectivity in these transformations originates from the steric repulsion of the aliphatic chain.

In the past a few decades, aryne chemistry has earned fruitful achievements in the areas of nucleophilic reactions, pericyclic reactions, and transition-metal-catalyzed reactions.[1] Recent advances in this field were greatly boosted by mild generation conditions for these highly reactive intermediates, i.e., the methods developed by Kobayashi[1f,g,2] and Hoye.[3] Toward aromatic compounds with over two substituents, however, a simple aryne intermediate cannot fulfill the task. Alternatively, building blocks that can generate multiple triple bonds on a benzene ring, i.e., benzdiyne[4] and benztriyne[5] equivalents, were investigated, which could furnish a benzene analog with up to six substituents. In view of the vast existence of natural products as well as drug molecules containing multifunctionalized arene structural motifs, the convenient, practical, and/or transition-metal-free production of these aromatic frameworks remains one of the top goals to pursuit.

As a recently emerged aryne intermediate, 3-triflyloxybenzyne (**i**) has been found versatile to prepare various multisubstituted arenes through the iterative generation of two aryne intermediates, namely 1,2- and 2,3-arynes (Scheme 1a).[6] Mechanistic perception of this process, however, reveals that *a nucleophile is necessary to act as the "vanguard" to attack intermediate* ***i*** in an S_N2' manner in order to trigger the following steps. In sharp contrast, whenever a pericyclic reaction takes place, both the 1- and 2-positions on **i** are locked simultaneously, which would then prohibit the generation of the 2,3-aryne intermediate.[7] Is it really obligatory that no second aryne could be produced after **i** is "locked" by its cycloadducts? Herein, we present our discovery on the convenient regioselective multifunctionalization of 3-triflyloxybenzyne (**i**), where its formal [2+2] cycloadducts with ketene silyl acetals (KSAs) could be readily converted to 2,3-aryne intermediates through Grob fragmentation.

It is worth mentioning that this protocol can readily reach phenylacetic acid framework that plays important pharmacological roles in medicines, such as Fexofenadine and a variety of pain relievers (Ibuprofen, Carprofen, Fenoprofen, and Bromofenec, etc.) (Figure 1). Further elaboration of the aliphatic side chain could afford benzoates or benzamides, such as the structure of anticancer drug Niraparib.[8]

Scheme 1. Background and Our Design



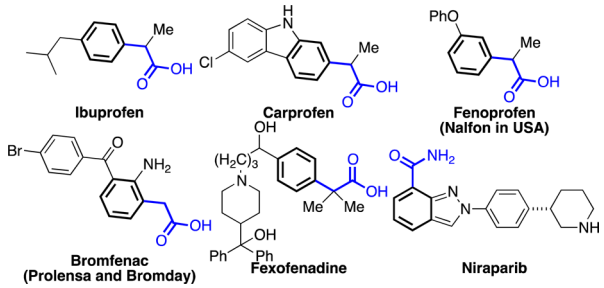


Figure 1. Selected medicines.

In line with our interest in the efficient preparation of multisubstituted arenes via aryne chemistry,[6,9] we were curious that, after 3-triflyloxybenzyne (**i**) undergoes [2+2] cycloaddition to form a four-membered ring, whether it is plausible to kick out the C3-OTf group and generate a 2,3-aryne intermediate. With this consideration in mind, we commenced our study by seeking possible further conversion means from the [2+2] cycloadduct of 3-triflyloxybenzyne (**i**). Upon ring opening, benzocyclobutenols

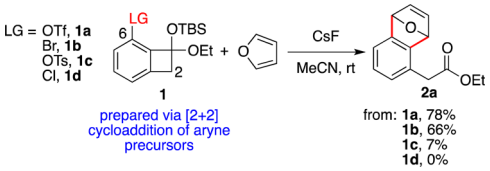
Received: November 25, 2016
Published: December 30, 2016

DOI: 10.1021/jacs.6b12161
J. Am. Chem. Soc. 2017, 139, 623−626

or benzocyclobutenones intend for either *distal* C−C bond cleavage (Scheme 1b, path a) or *proximal* C−C bond cleavage (Scheme 1b, path b). In general, thermolytic ring opening prefers path a via *o*-xylylene intermediates (Scheme 1c).[10] Recently, Dong[11] and others[12] developed transition-metal insertion approaches to these strained rings, which enabled the selective C−C bond cleavage via path b (Scheme 1d). As shown in Scheme 1e, we conceived that both the excellent leaving ability and electron withdrawing character of an OTf group might be able to alter the ring-opening means toward path b and result in the generation of 2,3-aryne species (also see Scheme 1b, X = OTf), the process of which is also seen as a Grob fragmentation.[13] Although Grob fragmentation is well-known to form alkenes and alkynes with numerous synthetic applications, this fragmentation approach has yet to be utilized in aryne generation.[14]

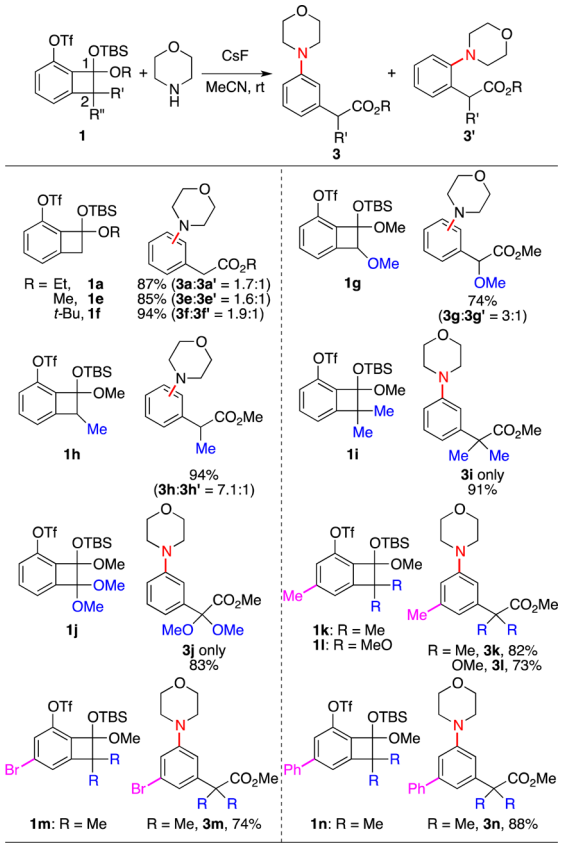
To test our hypothesis, we commenced our study by examining a series of [2+2] cycloadducts **1** prepared from 3-substituted benzynes and KSAs, the regioselective construction of which have been established by Suzuki and others[5,7a,15] (Scheme 2, also see Supporting Information for their preparation). Satisfyingly, when **1a** with an OTf as the leaving group (LG) was tested, its Diels−Alder reaction with furan afforded **2a** in 78% yield. Interestingly, **1b** with a 6-Br group could also afford **2a** in 66% yield. However, both **1c** and **1d** with 6-OTs and 6-Cl groups, respectively, either gave trace amount of **2a** or had no desired product at all. These results indicate that the groups on the C6 position of **1** dramatically affect aryne generation efficiency. To the best of our knowledge, this is the first example exhibiting the generation of an aryne intermediate via Grob fragmentation from a benzocyclobutenol analog along with the concomitant disconnection of three chemical bonds, namely O−Si, C−C, and C−O bonds. Because the OTf group is superior over other LGs in this transformation,[1f,g] in addition with the convenient preparation of **1a**, we decided to carry on our study using OTf as the leaving group.

Scheme 2. Study on Various Leaving Groups



After this ring opening, 2,3-aryne formation protocol was established, morpholine was chosen as the nucleophile to examine the reactivity of this method (Scheme 3). A challenge was encountered on this stage: there would be lack of regioselective control on intermediate **iii** (Scheme 1e) when **1a** is employed. Indeed, when **1a** reacted with morpholine, a mixture of regioisomers **3a** and **3a′** were obtained in a ratio of ~1.7:1. Similar ratios were also found with **1e** and **1f**, when a methoxy or a *tert*-butoxy group is present (Scheme 3). How to differentiate the two reaction sites on intermediate **iii**, namely the *meta*- and *ortho*-positions, in order to enhance the regioselectivity becomes an urgent demand for this work. Gratifyingly, gradually increasing the steric congestion on the C2-position (Scheme 3, **1g** to **1j**) could dramatically affect the *meta*-to-*ortho* selectivity and eventually reach the sole products **3i** and **3j**. Preliminary modeling study revealed that the excellent selectivity originates from the prominent steric repulsion of the bulky *gem*-dimethyl or

Scheme 3. Reactions of Morpholine with Aryne Precursors 1[a]



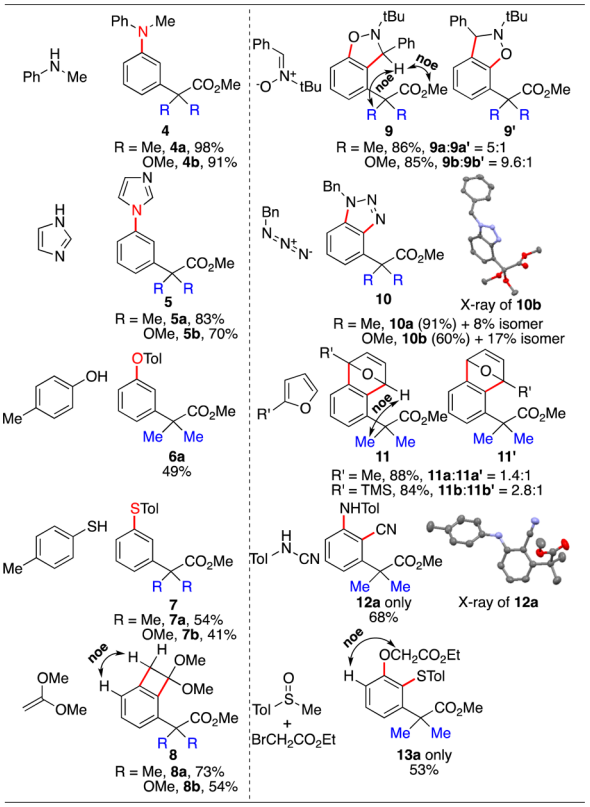
[a]Conditions: **1** (0.2 mmol), morpholine (0.4 mmol) and CsF (0.4 mmol) in MeCN (4 mL) at rt.

gem-dimethoxy groups. Although EW conductive effect has been extensively investigated in aryne chemistry to regulate the regioselectivity,[1c,16] there are only limited successes on steric repulsion-controlled aryne chemistry.[17] Moreover, compounds **1** with additional substituents, such as Me (**1k** and **1l**), Br (**1m**), and Ph (**1n**) groups, on the benzene ring were tested; all of them could afford the desired products in good to high yields with excellent regioselectivity.

After identifying both *gem*-dimethyl and *gem*-dimethoxy groups as the ideal regulation factors with morpholine, we proceeded to study their reactivity with various arynophiles. As shown in Table 1, different nucleophiles, such as *N*-methylaniline, imidazole, phenol, and thiophenol, could all afford the desired products **4**−**7** in distinct *meta*-selection. Because arynes are superior in making fused rings, we then tested different cycloaddition reactions with **1i** and **1j**. The formal [2+2] cycloaddition of 1,1-dimethoxyethene with **1i** and **1j** gave **8a** and **8b** in 73% and 54% yields, respectively, both of which showed excellent selectivity. [3+2] Cycloaddition with *N*-*tert*-butyl-*α*-phenylnitrone and benzyl azide afforded **9** and **10**, respectively, in good to high regioselectivities. However, when 2-methyl furan was reacted with **1i**, the reaction gave products **11a** and **11a′** in a ratio of 1.4:1. With an effort to increase the steric repulsion by using 2-trimethylsilyl furan as the substrate, the product ratio of **11b**:**11b′** only slightly enhanced to 2.8:1. Moreover, the insertion reactions of the generated 2,3-aryne with both *σ*-bond and double bond were tested. Single product **12a** was obtained in 68% yields when *p*-tolyl cyanamide[18] was utilized. In the presence of ethyl bromoacetate, aryne insertion into the S═

DOI: 10.1021/jacs.6b12161
J. Am. Chem. Soc. 2017, 139, 623−626

Table 1. Reactions with Aryne Precursors 1i and 1j

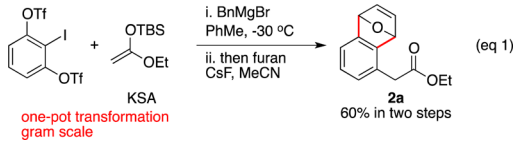


O bond of *p*-tolyl methyl sulfoxide[19] gave **13a** as the product in high selectivity and good yield as well. The structures of **10b** and **12a** were unambiguously determined by their X-ray single crystal analysis, and the stereochemistry of the other major products was determined by NOE study (Table 1).

To elucidate the relationship between reaction type and product structure, a close analysis of the examples in Table 1 disclosed that our approach has a tendency to give excellent *meta* selectivity whenever a nucleophile is employed or the first step of the reaction with the 2,3-aryne is *more or less nucleophilic*. For example, the formal [2+2] cycloaddition with arynes is known to be a first-step nucleophilic process,[5,15] which is also the same scenario with both aryl cyanamide and sulfoxide. In contrast, in the pericyclic transformations with furan derivatives, the ratios of products **11** are significantly diminished, indicating that the steric repulsion does not dramatically affect the regioselectivity in concerted processes. As for the [3+2] cycloadditions with phenylnitrone and benzyl azide, the medium product ratios might be attributed to an overall effect of the nucleophilic and the steric characters of these substrates.

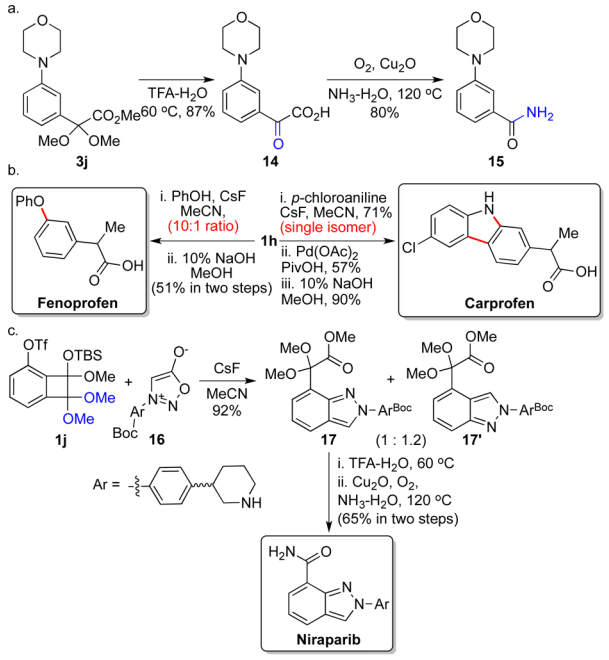
These examples are the first to exhibit that 3-triflyloxybenzyne (**i**) can be involved in unprecedented reaction sequences, namely cycloaddition−nucleophilic and cycloaddition−cycloaddition reactions. Moreover, with the success of this strategy, we wonder if we could track back this transformation to 3-triflyloxybenzyne (**i**) stage. As an exhibition, gram-scale of 3-triflyloxybenzyne (**i**) precursor was treated with KSA first and, upon reaction completion, CsF and furan were then added. Finally, **2a** was isolated in a total 60% yield in this one-pot process (eq 1).

Study on the phenylacetic acid framework of the products disclosed that this protocol could not only provide convenient further elaboration opportunities but also be used in practical synthesis of valuable molecules. It was noticed that the successful



utilization of *gem*-dimethoxy analog **1j** in this transformation is distinct, because this side chain could be converted to various other functional groups. As an exhibition, ketone acid **14** was readily obtained in 87% yield from compound **3j** in wet trifluoroacetic acid. Further decarboxylative conversion of **14** produced benzamide **15** in 80% yield (Scheme 4a).[20]

Scheme 4. Synthetic Elaboration



Consequently, the aliphatic side-chain from our ring-opening products could also be seen as an equivalent of either benzoate or benzamide, which shed the light on a broader spectrum of applications for this methodology.

Because phenylacetic acid is an important structural motif on many drug molecules, we picked Fenoprofen and Carprofen as our synthetic targets. As shown in Scheme 4b, Fenoprofen was synthesized in two steps from **1h**, and Carprofen was made in one extra step, both of which gave high regioselectivity in the ring-opening step. To exhibit further the synthetic applicability of our protocol, Niraparib was chosen, which is recently emerged as a potent antitumor PARP inhibitor, especially in the treatment of ovarian cancer.[8] As shown in Scheme 4c, [3+2] Cycloaddition of **1j** with **16** afforded **17** in 42% yield along with 50% of the other isomer **17′**. The following two-step one-pot conversion of **17** to benzamide using the conditions developed in Scheme 4a could afford racemic Niraparib in 65% overall yield. Although the regioselectivity in the [3+2] cycloaddition step is not satisfactory, the core of compound **17′** also shows PARP inhibition activity, the framework of which cannot be readily synthesized via traditional ways.[21] All of these examples suggest that our protocol is amenable and could be used in broad synthetic applications.

In summary, toward arene multifunctionalization, we have developed a unique protocol with 3-triflyloxyaryne intermediates, in which a chemoselective ring-opening method was

DOI: 10.1021/jacs.6b12161
J. Am. Chem. Soc. 2017, 139, 623−626

exquisitely designed from their [2+2] cycloadducts via Grob fragmentation in order to allow the generation of the consequent 2,3-aryne intermediate. This strategy is general, highly efficient, and transition-metal-free, which could be utilized in various combinations of arynophiles as well as in drug syntheses. The regioselectivity of this protocol is influenced by steric repulsion and preferentially favors nucleophilic-type transformations. Our ongoing work includes other synthetic applications of this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12161.

Experimental details for all chemical reactions and measurements and X-ray single crystallographic data (PDF)

Data for $C_{18}H_{19}N_3O_4$ (CIF)

Data for $C_{19}H_{20}N_2O_2$ (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge research support of this work by NSFC (21372268), Fundamental Research Funds for the Central Universities (106112016CDJZR228806), and Graduate Scientific Research and Innovation Foundation of Chongqing (Grant No. CYB16033).

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